

Seizure management and prescription patterns of anticonvulsants in Dravet syndrome: A multicenter cohort study from Germany and review of literature

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ABSTRACT

Objective: The aim of this study was to describe the treatment pattern of patients with Dravet syndrome (DS) in Germany with routine antiepileptic drugs (AEDs) and emergency medication, and to review the literature of real-world evidence on medicine utilization of patients with DS in Europe.

Methods: Patient use of routine AEDs and emergency medications over 3–6 months was analyzed from a 2018 multicenter survey of 93 caregivers of patients with DS throughout Germany. Results were contextualized in a review of real-world evidence on medicine utilization of patients with DS in Europe.

Results: The variety of medications and the most frequent combinations routinely used by patients with DS (AEDs and others) are described. Patients use a large number of pharmaceutical treatments to manage seizures. The five most commonly used AEDs were sodium valproate (66% of the patients; mean daily dose: 660 mg; 24.5 mg per kg bodyweight), bromide (44%; 1462 mg; 51.2 mg per kg), clobazam (41%; 10.4 mg; 0.32 mg per kg), stiripentol (35%; 797 mg; 27.6 mg per kg), and topiramate (24%; 107 mg; 3.5 mg per kg). Ninety percent had reported using emergency medications in the last 3 months; with the most common medications being Buccolam (40%, an oromucosal form of midazolam) and diazepam (20%, mostly rectal application). No discernible relationships between current medication and age or seizure frequency were observed.

Significance: This is the first comprehensive report of routine AEDs and emergency medication use in a large sample of patients with DS in Germany over a period of 3–6 months and shows that despite the most common

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AED combinations being in line with clinical guidelines/best practice, there is no discernable impact of best treatment on seizure frequency. We find a higher use of bromide in Germany compared with other real-world evidence in Europe.

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1. Introduction

Dravet syndrome (DS) is a rare form of epilepsy accompanied by impaired psychomotor and neurologic development; it is diagnosed clinically in the first year of life in apparently healthy infants [1]. Diagnosis has been facilitated by the discovery of the *SCN1A* gene's involvement in the condition [2] with around 85% of cases of DS estimated to be caused by *SCN1A* mutations [3].

Dravet syndrome is defined by febrile and afebrile generalized and unilateral, clonic or tonic-clonic seizures occurring before the patients' first birthday. Later seizure types include myoclonus, atypical absences, and focal seizures. All seizure types are resistant to treatment with anti-epileptic drugs (AEDs). Developmental delay becomes apparent within the second year of life and is marked by lifelong cognitive, behavior, and motor impairment [4]. After disease onset, patients may experience episodes of status epilepticus (SE) at any age, although the incidence peaks in the first decade of life [5]. Furthermore, ongoing episodes of SE will have a negative impact on the overall outcome [6,7].

Antiepileptic medications for the prophylactic treatment of seizures in DS are only partly effective [8,9], and sodium channel-blocking anti-convulsants such as carbamazepine and lamotrigine are contraindicated and have negative effects on cognitive outcome [10]. There were no medications specifically approved for DS until the introduction of stiripentol as an orphan drug for therapy-resistant DS, which has a marketing authorization in Europe for use in combination with sodium valproate and clobazam [11].

The lack of specific therapeutic options and of guidance on the management of DS is a factor motivating the development of a consensus-based set of guidance by Wirrell et al. [8], who found a strong consensus for stiripentol as second-line treatment in DS in line with its European Medicines Agency approval.

With stiripentol becoming a mainstay of treatment for DS [12,13], cannabidiol approved by the U.S. Food and Drug Administration (FDA) for use in DS in June 2018, and fenfluramine in development for the condition, it is a timely juncture to review utilization patterns for AEDs and other therapies in patients with DS.

The aim of this paper was to analyze and report further detail on the treatment pattern of patients with DS in Germany with routine AEDs and emergency medication previously reported in a German burden-of-illness study [14] and add these observations to a review on the literature of real-world evidence on medicine utilization of patients with DS in Europe.

2. Methods

2.1. Patients and methods

The study was designed as a cross-sectional, prospective multicenter survey and enrolled patients with DS and their caregivers throughout Germany (Bielefeld, Dresden, Erlangen, Frankfurt, Giessen, Hirschaid, Kiel, Kork, Münster, Tübingen, Vogtareuth) and through the German patient advocacy group (Dravet-Syndrom e.V., Markkleeberg, Germany). The study had ethics approval and was registered at the German Clinical Trials Register (DRKS00011894). The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were followed [15]. Further details of methodology and questionnaire design have been reported previously [14,16,17]. Caregivers of patients with DS completed paper questionnaires that

included questions about the patient's demographics, clinical characteristics, and healthcare resource utilization in the previous three or 12 months (high recall events only) and were completed between April 2017 and January 2018. Diaries were completed in real time for three months after the period covered by the questionnaire (latest April 2018) and consisted of a 12-week page-per-week diary to record day-to-day experiences of DS and associated healthcare utilization. Survey materials were distributed either at a meeting of the German DS advocacy group held in March 2017 or through neurologist appointments. After receiving written informed consent from the patients' parents or legal guardians, all patients with DS and their caregivers were deemed eligible. The seizure and epilepsy syndrome classifications were adapted to the latest definitions of the International League Against Epilepsy (ILAE) [18,19].

2.2. Survey questions on medication

Data from the survey represent routine medication use over a period of three months and emergency medication over a period of 6 months as follows: Caregivers reported current routine medication and retrospective, 3-month emergency medication use in the questionnaire returned to the study coordinators before commencing the 3-month prospective diary. For routine medication, the questionnaire asked: 'what medications are you currently taking (in current day)?', with the same question asked in the diary on the last day of the 12th week. For emergency medications, the questionnaire asked: 'what emergency medication have you taken in the last 3 months?' In the diary, respondents were asked each of the 90 days whether they administered emergency drugs and to name them.

2.3. Seizure frequency and age subgroups

Patients were grouped according to seizure frequency as follows [14]: at least once a day, at least once a week, at least once a month, at least once every six months, at least once a year, and no seizures for more than a year. These groups are mutually exclusive. In our analysis, the three most frequent categories were combined to obtain a cumulative percentage for those experiencing at least one seizure a month (Fig. 1). Patients were grouped according to age as follows: infants (aged 0 or 1 year; constituting 5% [5/93] of the patient population), preschool (aged 2–5 years; 30% [28/93]), middle childhood (aged 6–11 years; 30% [28/93]), in adolescence (aged 12–17 years; 20% [19/93]), and adults (aged 18 years and above; 14% [13/93]).

2.4. Statistical analysis

Response frequencies and the mean, standard deviation (SD), median ranges, and 25th and 75th quartiles of variables of interest were summarized using descriptive statistics. Statistical comparisons between groups were performed using chi-square tests, and a $p < 0.05$ was considered as significant. Statistical analysis was conducted with IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA).

3. Results

The questionnaires were completed by 93 carers of patients with DS of a median age of 8.5 years (mean: 10.1, SD: 7.1, Q25–Q75: [4.5–14.2]), the majority of which (86%) were aged under 18 years. Across all

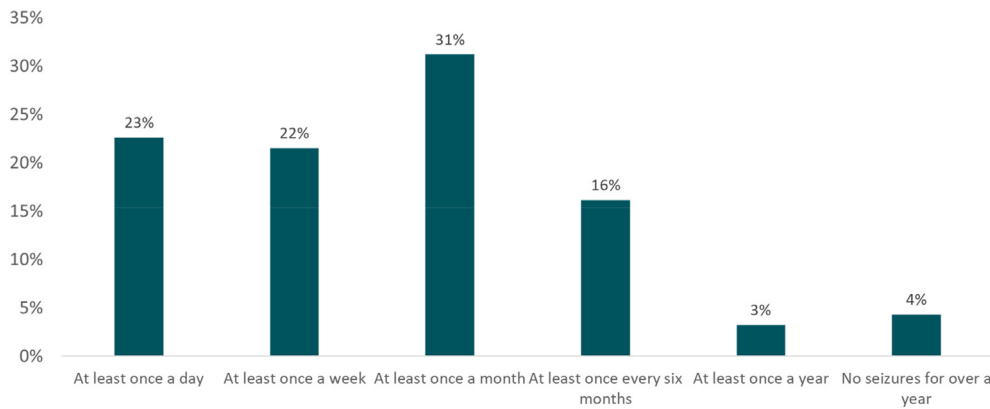


Fig. 1. The percentage of patients experiencing a given seizure frequency (source: questionnaire, $n = 93$). Seizure frequency groups are mutually exclusive.

patients and seizure types, the proportion of all patients experiencing at least one of any type of seizure per month was 76% and experiencing at least one generalized tonic–clonic seizure was 64%. In addition, 44% of patients experienced a seizure at least once a week and 23% at least once a day (36% and 6% for generalized tonic–clonic seizures), please also refer to Fig. 1. Seventy-seven percent of patients in this cohort had experienced SE at least once in their lives as reported before [14].

The results reported here are drawn from the questionnaire ($n = 93$) with the exception of the analysis of different AED regimens, for which questionnaire and diary responses ($n = 75$) were compared for validity.

3.1. Medicine utilization

3.1.1. Routine antiepileptic drugs

Ninety of the 93 (97%) patients used routine anticonvulsant medications. As reported in Strzelczyk et al. [14], the most commonly prescribed drugs were valproate, bromide, clobazam, stiripentol, and topiramate. Details of use are provided in Fig. 2 and Table 1.

Although stiripentol is a relatively recent addition to the AED options approved by the European Medicines Agency (EMA), it was used in over one-third of patients. Cannabidiol and fenfluramine were used in three patients each, despite neither being licensed for general use at the time of the survey. Fenfluramine was available as study medication only, and cannabidiol as either in a phase 3 study setting or as an individual healing attempt applied for in advance and approved by the health insurance company. Patients receiving either of these two therapies were treated in the experimental setting, the dosing of cannabidiol was low as compared with the studied dosing of 10 to 20 mg per kg bodyweight. The three patients not using routine anticonvulsant medications reported at least one seizure (any type) every six months ($n =$

1), every month ($n = 1$), or every week ($n = 1$). One of these three patients was on ketogenic diet.

The most frequently used AEDs of patients with high seizure frequency (weekly or more frequent generalized tonic–clonic seizures, $n = 34$) were compared with those with low seizure frequency (patients who reported no seizures in the last 6 months, $n = 7$). A greater proportion of patients with low seizure frequency used levetiracetam (43% vs 10%), and none used stiripentol and clobazam (0% for both vs 38% and 50%, respectively) compared with patients with high seizure frequency (Fig. 3), although the numbers of patients are too small to draw statistically firm conclusions.

3.1.2. Treatment regimens

The majority of patients took a combination therapy of several anticonvulsants. Sodium valproate, stiripentol, and clobazam (VSC) was the most commonly used treatment regimen in both the questionnaire [13] and diary sample (16% and 8%, respectively). The second most commonly used treatment regimen was sodium valproate alone (6% and 5%, respectively), followed by valproate and topiramate (4% and 4%), valproate and levetiracetam (4% and 3%), valproate, bromide, and clobazam (4% and 0%), valproate, bromide, and topiramate (3% and 5%), and clobazam, bromide, and stiripentol (3% and 5%).

Of the top seven most common AED regimens, valproate alone or in combination with other AEDs featured in six of them (one monotherapy, two dual therapy combinations, and three triple therapy combinations). Stiripentol was used in combination with either valproate and clobazam (the European public assessment report refers to stiripentol as add-on therapy to treat generalized tonic–clonic seizures inadequately controlled by the dual therapy regimen alone) or bromide and clobazam (Fig. 4).

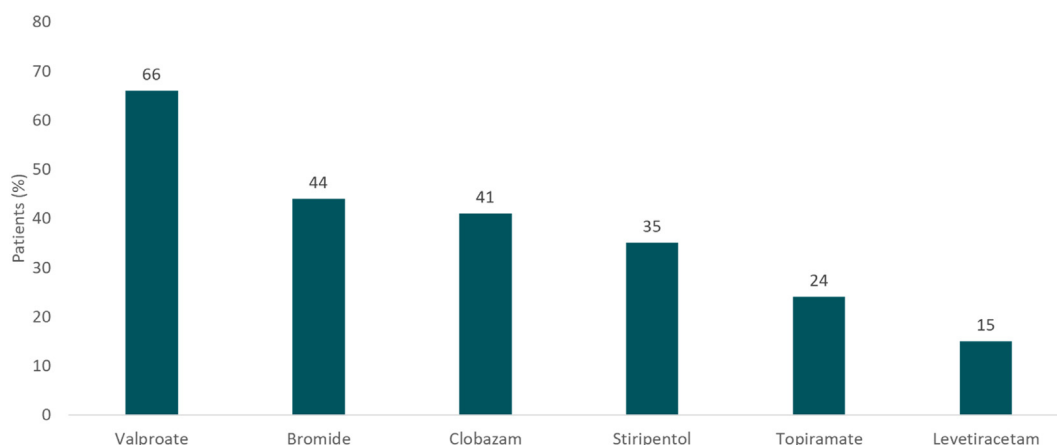


Fig. 2. The six most frequently used AEDs by frequency of use (%) (source: questionnaire, $n = 93$).

Table 1
Utilization of routine AEDs among patients and costs over three months (questionnaire, n = 93).

Prescribed medication	N (n = 93)	Mean daily dose (mg)	Standard deviation (mg)	Minimum (mg)	Median (mg)	Maximum (mg)	Mean daily dose per body weight (mg/kg)	Median daily dose per body weight (mg/kg)	Mean costs per user per day (€)	Standard deviation (€)
Valproate	61	660.3	408.59	120	600	2000	24.48	23.68	0.43	0.26
Bromide	41	1462.5	855.1	425	1300	3825	51.22	46.15	0.92	0.54
Clobazam	38	10.43	8.16	2	10	50	0.32	0.34	0.52	0.41
Stiripentol	33	797.12	529.42	200	600	2250	27.55	24.26	17.52	11.63
Topiramate	22	106.99	83.51	10	87.5	400	3.48	2.94	1.27	0.99
Levetiracetam	14	1381.43	1354.36	240	925	5000	43.19	41.67	6.55	6.42
Cannabidiol ^a	3	270		270	270	270	20.77	20.77	11.05	5.97
Zonisamide	3	208.33	137.69	50	275	300	5.39	5.77	9.63	6.36
Ethosuximide	3	516.67	225.46	300	500	750	27.83	27.78	1.37	0.60
Sulthiame	3	316.67	28.87	300	300	350	6.55	7.14	2.45	0.22
Fenfluramine	3	7.67	2.52	5	8	10	0.21	0.19	Not available on the market	
Lacosamide	2	325	106.07	250	325	400	6.26	6.26	12.68	4.14
Clonazepam	2	12.5	14.14	2.5	12.5	22.5	0.78	0.78	4.53	5.12
Primidone	1	500		500	500	500	4.76	4.76	0.34	0.00
Acetazolamide	1	500		500	500	500	7.14	7.14	0.86	0.00
Fluoxetine	1	21		21	21	21	0.60	0.60	0.41	0.00
Lamotrigine	1	450		450	450	450	6.25	6.25	1.03	0.00
Perampanel	1	4		4	4	4	0.20	0.20	10.12	0.00
Oxcarbazepine	1	1800		1800	1800	1800	25.00	25.00	3.39	0.00
Mesuximide	1	600		600	600	600	14.29	14.29	2.56	0.00
Rufinamide	1	1800		1800	1800	1800	38.30	38.30	13.71	0.00

^a Two cannabidiol patients reported using cannabis oil and did not report cannabidiol dosages.

3.1.3. Patient age and treatment regimen

Considering the mean number of drugs used, and the most frequently used drug across patient groups defined according to age group and frequency of seizures, there was no clear relationship between age or seizure frequency and number or type of medicine used (Table 2). In the 'at least once per week' and 'at least once per month' seizure frequency groups, the data suggest that older patients may use more drugs than younger patients, but the numbers of patients are too small to draw statistically firm conclusions. Similarly, while there were tentative indications that the number of medicines per patient declines with decreasing frequency of seizures, the evidence on this relationship was unclear.

Valproate was the most frequently used AED among all of the defined age groups. It was used across ranges of seizure frequency, although it was not one of the most frequently used AEDs in those experiencing at least one seizure a day, with clobazam and bromide being more common AEDs in this group. Stiripentol was one of the

most common treatments in preschool patients experiencing a seizure at least once per week and adolescents experiencing a seizure at least once per month. While levetiracetam was a component of one of the most frequently used drug regimens overall (in combination with valproate), it was used in only a dozen patients altogether (Table 2). Of the patients who returned both the questionnaire and diary (n = 75), 72% reported using the same AED combination in the questionnaire and diary. An additional 5% also reported the same combination with the addition of fenfluramine in the diary.

3.1.4. Emergency medications

Around 90% of questionnaire respondents (n = 84) had reported using one or more emergency medications in the last three months. The median age for users of emergency medications was 8.2 (mean: 9.8, SD: 7.0, Q25–Q75: [4.2, 14.1]) years with a range of 1–33. The most common stated in the questionnaire (37 patients) was Buccolam, an oromucosal form of midazolam. Overall, the most commonly used

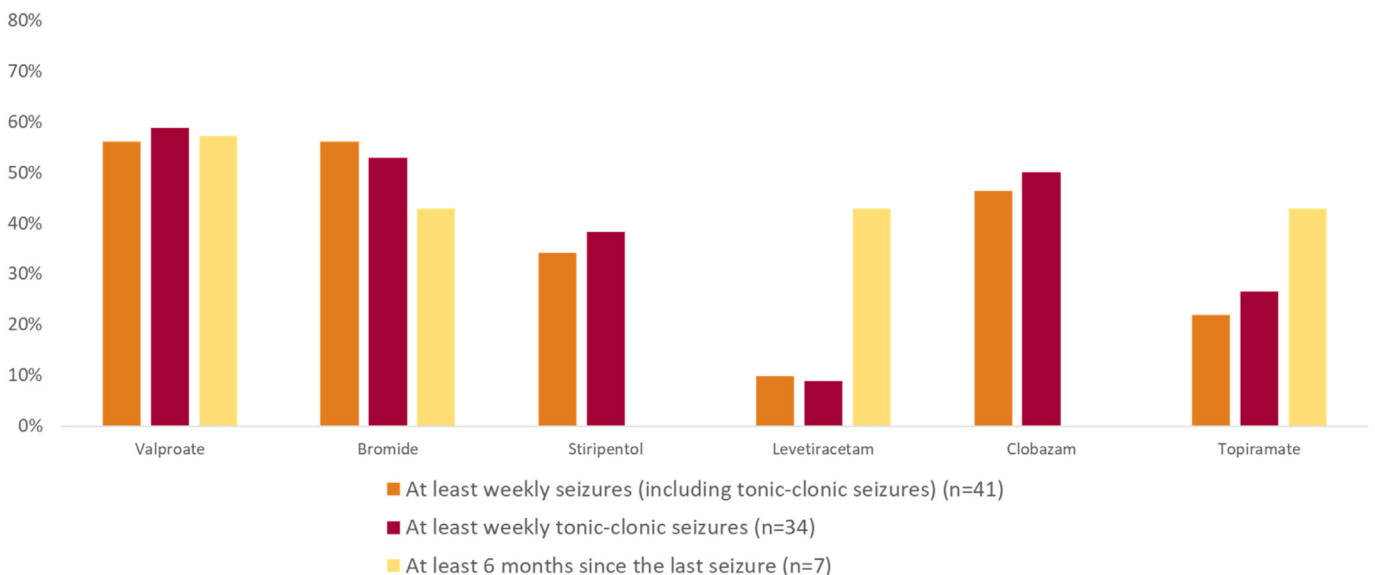


Fig. 3. Individual AEDs by frequency of use (%) in patients with high seizure frequency (weekly or more frequent seizures [all types] or generalized tonic-clonic seizures) or low seizure frequency (no seizures in the last 6 months) (source: questionnaire, n = 93).

	Valproate	Bromide	Clobazam	Stiripentol	Topiramate	Levetiracetam
Valproate users (n=61)		43%	41%	39%	21%	10%
Bromide users (n=41)	63%		37%	27%	27%	7%
Clobazam users (n=38)	66%	39%		71%	18%	11%
Stiripentol users (n=33)	73%	33%	82%		12%	9%
Topiramate users (n=22)	59%	50%	32%	18%		5%
Levetiracetam users (n=14)	43%	21%	29%	21%	7%	

Fig. 4. Proportion of AEDs used concurrently (source: questionnaire, n = 93). Red refers to proportions $\geq 55\%$, $< 55\%$; orange $\geq 35\%$, $< 35\%$; yellow $\geq 15\%$; $< 15\%$; blue.

emergency medications were benzodiazepines/benzodiazepine derivatives, such as clonazepam, diazepam, and midazolam nasal spray (Table 3). The median age for Buccolam users was 5.4 years (mean: 7.5, SD: 5.7, Q25–Q75: [3.3, 14.1]) with a range of 1–22.

3.1.5. Dietary management

In addition to AEDs and emergency medicines, patients also used diet to manage their condition as previously reported [14]. Seven different types of diet were identified, with ten respondents using a ketogenic

Table 2

Number of drugs and most frequently used drugs (as monotherapy or multidrug regimen) by age group and seizure frequency (source: questionnaire).

Age group/seizure frequency ^a	Infants (<2 years)	Preschool (2–5 years)	Middle childhood (6–11 years)	Adolescence (12–17 years)	Adult (=; ≥ 18 years)	Total patients
At least once per day						
No. of patients	0	6	8	4	3	21
Medicines/patient	N/A	2.67	2.75	3.25	2.33	2.76
Most commonly used medicines (independent of regimen)	N/A	Bromide	Clobazam	Clobazam	Bromide	Bromide
No. of patients using most commonly used drug	N/A	4	6	3	2	13
At least once per week						
No. of patients	0	3	7	7	3	20
Medicines/patient	N/A	1.00	2.29	3.43	3.67	2.7
Most commonly used medicines (independent of regimen)	N/A	Bromide, stiripentol, cannabidiol	Valproate	Bromide	Valproate, clobazam	Valproate
No. of patients using most commonly used drug	N/A	1, 1, 1	5	5	3	12
At least once per month						
No. of patients	2	12	7	5	3	29
Medicines/patient	1.50	2.67	2.86	2.40	3.00	2.62
Most commonly used medicines (independent of regimen)	Valproate	Valproate	Valproate, clobazam, topiramate	Stiripentol, clobazam	Valproate, clobazam	Valproate
No. of patients using most commonly used drug	2	10	4, 4, 4	3, 3	2, 2	20
At least once every six months						
No. of patients	3	7	4	1	0	15
Medicines/patient	1.67	2.00	2.25	N/A	N/A	2
Most commonly used medicines (independent of regimen)	Valproate	Valproate	Valproate	N/A	N/A	Valproate
No. of patients using most commonly used drug	3	7	3	N/A	N/A	13
At least once a year						
No. of patients	0	0	0	1	2	3
Medicines/patient	N/A	N/A	N/A	2	2	2
Most commonly used medicines (independent of regimen)	N/A	N/A	N/A	Levetiracetam, acetazolamide	Bromide	Bromide
No. of patients using most commonly used drug	N/A	N/A	N/A	1, 1	2	2
Over a year between seizures						
No. of patients	0	0	2	1	1	4
Medicines/patient	N/A	N/A	2	3	3	2.5
Most commonly used medicines (independent of regimen)	N/A	N/A	Valproate	Valproate, bromide, topiramate	Levetiracetam, lamotrigine, oxcarbazepine	Valproate
No. of patients using most commonly used drug	N/A	N/A	2	1, 1, 1	1, 1, 1	3
Total patients	5	28	28	19	12	92

^a The seizure frequency groups defined in this table are mutually exclusive.

Table 3
Utilization of emergency medications and average costs over three months (questionnaire, n = 93).

Emergency medication	n	Frequency of use per 3 months	Mean dose per application (mg)	Minimum (mg)	Median (mg)	Maximum (mg)	Mean dose per kg body weight (mg/kg)	Median dose per weight (mg/kg)	Mean costs per 3 months per user (€)	SD (€)
Buccolam	37	5.5	7.4	2.5	7.5	20.0	0.28	0.26	116.09	197.68
Midazolam nasal spray	5	4.6	5.4	2.5	5.0	7.5	0.24	0.27	14.78	8.75
Chloralhydrate	4	8.5	994.0	20.0	1000.0	2000.0	38.27	34.29	10.63	13.07
Diazepam rectal	16	3.8	7.5	5.0	7.5	10.0	0.38	0.34	29.09	37.04
Diazepam oral	3	8.0	7.0	5.0	5.0	10.0			1.92	2.51
Lorazepam oral	4	3.8	1.4	1.0	1.0	2.5			0.65	0.55
Clonazepam oral	7	7.5	1.0	0.5	1.3	1.3			5.20	5.7
Other	5	4.5							223.72	443.79

diet (an option mentioned in the Association of the Scientific Medical Societies in Germany: *Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften* (AWMF); and *National Institute of Health and Care Excellence* (NICE) guidelines) and other low carbohydrate diets. Five other types of diet were used by one respondent each.

4. Discussion

This survey is the first study to measure the patterns of medicines and other resource use of DS over a period of up to 6 months using both retrospective and prospective methodology in a German sample of patients with DS and adds to the previous reports of AED use in patients with DS in Europe [12,13,20], summarized in Table 4.

The sample was concentrated in preschool, middle childhood, and adolescence and included some adult patients, with the proportion experiencing a seizure once a month or with greater frequency peaking in adolescence. This sample of patients shows some of the typical features of DS, with multiple seizure types and epilepsy course, and is comparable with previous real-world evidence studies [12,21]. A high seizure frequency is characteristic of patients with DS, although less than half (44%) experienced a seizure at least once a week, and 37% a generalized tonic-clonic seizure with this frequency. Similar findings have been reported in a primarily European study by Aras et al. in which “only 45%” of the sample had more than four generalized tonic-clonic seizures per month on average, but with a wide range between countries studied (26%–67%) [12]. The distribution by age was comparable in the two studies, with the 15% of responders being adults in Aras et al. [12] comparable with the 13 of 93 patients in the current study.

Antiepileptic drug utilization showed similarities between Aras et al. and the current study. Aras et al. observed that a large number of therapies had been tried in their sample but that utilization was concentrated in a relatively small number of drugs [12]. Among their patients, treatment centered largely on five drugs: valproate, clobazam, topiramate, stiripentol, and levetiracetam, with 86%, 55%, 44%, 42%, and 22% using these AEDs as current therapy. Valproate was the most commonly used AED in the current sample at 66% while 41%, 35%, 24%, and 15% used clobazam, stiripentol, topiramate, and levetiracetam, respectively. In the survey by Villas et al., stiripentol was less commonly used, although as the data refer to medications ever used, this could be explained by its relatively recent availability (and its 36% utilization is similar to the 35% current usage in the analysis reported here) [13]. A similar list of top five treatments emerges in a European study by Lagae et al., where the most frequently used AED treatments were the following: valproate, clobazam, stiripentol, topiramate, and bromide, with 76%, 53%, 47%, 34%, and 10% using them, respectively [20]. The use of bromide was also found in our patient population as the second most used AED treatment.

Since it received its marketing authorization in Europe in 2007, the survey evidence indicates that stiripentol (the only drug specially approved in Europe for DS) is now a mainstay of treatment in EU states. In addition to evidence from pivotal clinical trials, its use is supported by real-world evidence of its effectiveness and cost impact [22,23] and, in the consensus statement by Wirrell et al. [8], is identified as one of two optimal second-line medications (the other being topiramate). This is a finding repeated in this sample, with stiripentol featuring in the most commonly used AED combination therapy.

In line with the evidence on their use individually, VSC was the most frequently used combination therapy in Aras et al. [12], with 29% using

Table 4
Review of real-world evidence on medicine utilization of patients with Dravet syndrome in Europe.

Study	Present study	Aras et al. <i>Epilepsy Behav</i> 2015	Villas et al. <i>Epilepsy Behav</i> 2017	Lagae et al. <i>Dev Med Child Neurol</i> 2018
Year of survey	2017/18	2014	2016	2016
Country	Germany	Europe-wide	Worldwide (18% Europe)	Worldwide (92% Europe)
Number of patients	93	274	256	584
Age of patients	Mean: 10.1	Median group: 4–8	Median group: 7–10	Mean: 10.6
Seizure frequency ^a	Gen. tonic-clonic (73%) Myoclonic (48%) Absence (23%) Partial/focal (22%) Atonic/drop attack (23%) [per 3 months]	Gen. tonic-clonic (78%) Myoclonic (42%) Absence (24%) Partial/focal (33%) Atonic/drop attack (14%) [per month]	N/A	Gen. tonic-clonic (78%) Myoclonic (49%) Absence (50%) Partial/focal (39%) Atonic/drop attack (26%) [per 3 months]
Most used AEDs	1. Valproate (66%) 2. Bromide (44%) 3. Clobazam (41%) 4. Stiripentol (35%) 5. Topiramate (15%)	1. Valproate (86%) 2. Clobazam (55%) 3. Topiramate (44%) 4. Stiripentol (42%) 5. Levetiracetam (22%)	1. Valproate (89%) 2. Clobazam (79%) 3. Topiramate (75%) 4. Lamotrigine (44%) 5. Stiripentol (39%)	1. Valproate (76%) 2. Clobazam (53%) 3. Stiripentol (47%) 4. Topiramate (34%) 5. Bromide (10%)
Most used emergency medication	1. Buccolam (40%) 2. Diazepam (20%) 3. Clonazepam (8%) (within 3 months)	N/A	1. Diazepam (94%) 2. Lorazepam (70%) 3. Midazolam (68%) (within the past)	N/A

^a For the present study, frequencies for the diary population are reported.

these three drugs together (with and without other AEDs) while 12% of patients used VSC (without other AEDs), also the most common combination in the current survey. In both studies, three and four drug regimen combinations were common, being used by 40% and 25%, respectively, in Aras et al. [12] compared with 34% and 22% in the current study. The most common emergency medications reported in this study were Buccolam (an oromucosal form of midazolam) (40%) and diazepam (20%) in a three-month period. Third and fourth, oral clonazepam and intranasal midazolam were reported, however, the latter is not commercially available and must be manufactured as a custom-made product [24]. While no other European study has reported emergency medication use in a three-month time frame, a worldwide study (18% participants residing in Europe) reported diazepam and midazolam as the most used medications in the past (94% and 68%, respectively) [13].

Overall, AED use in this sample was found to be high compared with patients with other epilepsies [25]. The average patient with DS both showed higher numbers of AEDs taken compared with other patients with epilepsy, and the cost of medication use was found to be higher among patients with DS than patients with other forms of epilepsy. The full burden of illness for DS was calculated in Strzelczyk et al. [14]. Antiepileptic drug costs were the third largest single cost item over a three-month period (mean: €892 per person, median: €532) after inpatient costs (mean: €1702, median: €0) and care grade allowances (mean: €1130, median: €1374). Although the use of emergency services was a regular occurrence in these patients, emergency transportation and emergency medicines made a relatively small contribution to overall costs, at €121 (median: €0) and €53 (median: €0), respectively, over a three-month period. Across all 93 questionnaire respondents, the mean (out of pocket) cost of diet was around €57 (median: €0) over three months but mean cost for the 12 respondents using special diets was €438 (median: €350), ranging up to €1050 over the period [14].

Differences between the data reported by the (retrospective) questionnaire and the (prospective) diary, while being a function of the differences in the samples of respondents, may also be reflective of some fluidity in the use of AEDs to manage DS. The top five most common regimens reported in the questionnaire and the top five from the diary gave a total of seven different regimens, all of which showed some use in both apart from the valproate/bromide/clobazam combination that had no recorded usage in isolation in the diary.

The dynamics of therapy are illustrated in previous studies by the case of levetiracetam, which emerges as a more significant historical than current treatment. In the full Aras et al. [12] sample, it was the most common 'ever used' AED, having been tried by over 50% of patients while in Villas et al. [13], it was the second most frequently used and, in addition to valproate, clobazam, and topiramate, had been used at some time by 79% or more of respondents. Changes in utilization over time could perhaps be driven by differences in effectiveness or perceived effectiveness. By way of illustration, the Villas et al. [13] study found that levetiracetam received a relatively low caregiver ranking of efficacy while the Wirrell et al. consensus statement rated it as only 'moderately effective' [8].

One of the main differences between this study and previous studies was in the use of bromide, which was the second most frequently used AED in the current study, being a part of current treatment in 44% of patients, and being used in three of the most common AED regimens. This is in line with previous studies from Germany [26,27] and other countries where bromide is available like Japan [28,29]. The frequent use of bromide in our study may reflect a difference in treatment patterns in Germany compared with recent wider European studies reporting 11% [12] and 10% [20]. Similarly, bromide had been tried at any time by only 14% of the Villas et al. sample [13]. The Wirrell et al. guidelines [8] concluded that there was no consensus on the efficacy of bromides, and it was rated below the three or four most commonly used AEDs for effectiveness in the Villas et al. study [13].

Whereas uncertainty exists about the role of bromides in treating DS, there is greater agreement about the inappropriateness of specific

therapies in DS, notably carbamazepine, oxcarbazepine, and lamotrigine, which Wirrell et al. recommend be avoided [8]. In patients with DS with *SCN1A*-related seizure phenotypes, the use of contraindicated medications has been found to be associated with negative effects on cognitive outcome [10]. Reassuringly, the latter two medications received only one mention each in the present study while carbamazepine received no mentions. However, the earlier surveys indicated that these therapies have frequently been tried in DS. Aras et al. [12] found that oxcarbazepine had been tried in 12% of cases and carbamazepine and lamotrigine by over one-third of patients while in Villas et al. [13], carbamazepine and oxcarbazepine had at one time been used in the management of over one-third and lamotrigine in nearly half of patients.

A notable number of patients in this study (16%) were following a specific (mostly ketogenic) diet in the past three months and confirms previous evidence that patients with DS use other approaches to manage their condition including the ketogenic diet which, in the Villas et al. study [13], was given the third highest effectiveness rating being valproate and stiripentol. This sample showed slightly higher levels of use of the ketogenic diet than a pan-European study did (6.5%) [20]. Interestingly, the fourth highest rated treatment was cannabidiol/medical marijuana, a treatment which, along with fenfluramine, has been reported in previous surveys but which (like fenfluramine) currently has no marketing authorization in Europe (cannabidiol received FDA approval in June 2018).

5. Conclusion

This survey has confirmed the finding of previous studies that treatment centers on a small number of key therapies despite the number of AEDs potentially available for, and tried by, patients with DS. Despite the evidence for the positive impact on DS of these therapies, the burden of DS in terms of seizures and comorbidities remains substantial. It is, therefore, hoped that new therapies in development can demonstrate meaningful benefits in this patient group and thus become adopted, as stiripentol has done [30], as important components in the management of DS.

Declaration of Competing Interest

SSB reports personal fees from UCB, Desitin Arzneimittel, Novartis, Zogenix, LivaNova, and Eisai.

AW-K reports personal fees from Desitin Arzneimittel, Dr. Schär, Novartis, Nutricia, VitaFlo, UCB Pharma.

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GKu reports personal fees from UCB Pharma, Desitin Arzneimittel, Zogenix, LivaNova, Eisai, GW Pharma, Bial, Dibropharma, Novartis, Biogen, Actelion.

GKl reports personal fees from Desitin Arzneimittel, Eisai, and Zogenix.

KMK reports personal fees from UCB Pharma, Novartis Pharma AG, Eisai, and GW pharmaceuticals.

LK reports travel support from UCB and Eisai.

TB reports fees from Desitin Arzneimittel, GW Pharma, and Zogenix.

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AS reports personal fees and grants from Desitin Arzneimittel, Eisai, GW Pharma, LivaNova, Medtronic, Sage Therapeutics, UCB Pharma, and Zogenix.

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Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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